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DEPARTMENT OF PUBLIC HEALTH AND SOCIAL SERVICES
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January 28, 2022

STANDING ORDER FOR PAXLOVID™

Purpose:

To reduce morbidity and mortality of the SARS-CoV-2 virus Paxlovid™ is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. As updated, the Public Readiness and Emergency Preparedness Act (PREP Act) and the conditions of this protocol apply.

High-Risk Criteria:

COVID-19 therapeutics are a critical part of Guam's COVID-19 emergency response. These treatments are provided freely by the Federal Government to the Department of Public Health and Social Services ("DPHSS") for its use and/or distribution within the Territory. Treatment is indicated for recently diagnosed COVID-19 patients with mild-moderate symptoms. Prescribing providers are advised to document SARS-CoV2 viral test (lab-based antigen or PCR), symptoms of COVID-19 for ≤ 5 days and be at high risk for progressing to severe COVID-19.

Due to limited available supplies prescribing physicians are advised to risk stratify based on the following criteria:

Highest-Priority:

- Not fully vaccinated; and
- Over the age of 50; and
- Has one or more comorbidities associated with increased risk of severe illness, hospitalization, or death referenced in https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html; or
- Pregnant

High-Priority:

- Fully vaccinated; and
- Over the age of 65; and
- Has two or more comorbidities associated with increased risk of severe illness, hospitalization, or death referenced in https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

Checklist Tool for Prescribers:

Patient Eligibility:

- ☐ Lab-based antigen or PCR Positive for SARS-CoV-2 test
- ☐ Age ≥ 18 years
- ☐ Alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate
- ☐ High-Risk criteria met (see above)
- ☐ Symptoms consistent with mild to moderate COVID-19
- ☐ Symptom onset within 5 days*
- ☐ Not hospitalized due to COVID-19

*Prescriber is encouraged to include a note to the pharmacist in the prescription stating: Please fill prescription by _____[insert date]_____. This prescription fill by date is within 5 days from symptom onset and complies with the patient eligibility criteria under the EUA.

All Patients:

- ☐ Provide electronic or hard copy of patient fact sheet
- ☐ Document that patient has received an electronic or hard copy of the patient fact sheet
- ☐ Review the information contained within the patient factsheet with the patient and counsel patient on the known and potential benefits and risks.

Prescribers and Pharmacsists are advised to review Emergency Use Fact Sheets attached herein and prescribe in accordance with the Emergency Use Authorization for Paxlovid™.

Paxlovid™:

On December 22, 2021 the FDA issued an EUA for the use of Paxlovid™. The EPIC-HR, a phase 2/3 randomized placebo-controlled trial in non-hospitalized high-risk adult patients with symptomatic COVID-19 demonstrated an 88% reduction in hospitalization and death in those taking paxlovid versus placebo within 5 days of symptom onset. Nirmatrelvir (PF-07321332) inhibits the SARS-CoV-2 protease and inhibits protein synthesis and viral replication. Nirmatrelvir is co-packaged with ritonavir which helps "boost" levels of nirmatrelvir. Ritonavir has been used in this capacity to treat HIV disease. Drug interactions are common with ritonavir and must be reviewed prior to prescribing. Paxlovid™ may lead to persons with HIV-1 developing HIV protease inhibitor resistance if given without complete antiretroviral therapy.

Treatment with Paxlovid™ is contraindicated in the following patients:

- History of hypersensitivity reactions to a ritonavir

- Patients on other medications relying on CYP3A for clearance (e.g., alfuzosin, amiodarone, flecainide, colchicine, clozapine, ergot derivatives, lovastatin, simvastatin, sildenafil (Revatio®) when used for pulmonary arterial hypertension) where elevated drug levels are associated with serious or life-threatening reactions.

Please review Section 4 of the Fact Sheet for Healthcare Providers.

• Patients on other medications which are CYP3A inducers (e.g., anticonvulsants like carbamazepine, phenobarbital, phenytoin; rifampin, St. Jon's Wort) which can decrease Paxlovid™ concentrations and potentially decrease potency of Paxlovid or lead to resistance. Please review Section 4 of the Fact Sheet for Healthcare Providers.

• Patients with kidney disease (eGFR < 30 mL/min) or Childs-Pugh Class C liver disease MSHS COVID-19 Treatment Guidance January 18, 2022

Caution must be used with multiple other medications including but not limited to calcium channel blockers, oral contraceptives, immunosuppressants commonly used in organ transplantation and hematopoietic stem cell transplantation, antifungals, chemotherapeutics, corticosteroids, and anticoagulation.

Please review Section 7 of the Fact Sheet for Healthcare Providers and your patient's medications prior to prescribing.

Paxlovid™ can be considered in the treatment of symptomatic adults and pediatric patients (≥ 12 years of age weighing at least 40 kg or 88 pounds) who have tested positive for SARS-CoV-2 infection. The patient/caregiver must be informed of the following prior to prescribing:

• Paxlovid™ is not FDA-approved and its use is authorized for emergency use by the FDA.

• There are no approved treatments for mild-moderate COVID-19, however other agents are authorized for similar indications under emergency use

• Please give patient a hard copy of the Fact Sheet for Patients and Caregivers

Due to limited supply, DPHSS advises prioritization when prescribing. Outpatient pharmacies capable of filling prescriptions have been designated by DPHSS.

• Patients must be symptomatic and able to start treatment within 5 days of symptom onset. Symptom onset must be documented in the pharmacist note section of the prescription order*

> *Prescriber is encouraged to include a note to the pharmacist in the prescription stating: Please fill prescription by _____[insert date]_____. This prescription fill by date is within 5 days from symptom onset and complies with the patient eligibility criteria under the EUA.

• Patient must be considered at increased risk for severe COVID-19 and fulfillment of prescription will be based on supply and prioritization by DPHSS

• In the pharmacist note section, document race/ethnicity from the following options: Asian/Native Hawaiian or other Pacific Islander; Black; Hispanic/Latino; native American/Alaskan Native; and White

• If you feel that your patient meets criteria and does not have a contraindication to the use of

molnupiravir as an alternative, you can write a similar prescription with the same details and include "To be used in case Paxlovid™ prescription cannot be filled because of supply limitation."

Dosing: 300 mg of nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice a day for a total of 5 days. The medications can be taken with or without food These medications must be swallowed whole and CANNOT be chewed, broken or crushed. For patients with eGFR ≥ 30 to < 60 mL/min, the dose must be adjusted: 150 mg of nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir If the patient misses a dose of Paxlovid™ within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time.

Caution:

- Use of Paxlovid™ and certain other drugs may result in significant drug interactions. Please review Section 7 of the Fact Sheet for Healthcare Providers and your patient's medications prior to prescribing. This link can be used to assess for drug interactions.

- Hepatotoxicity has occurred in patients receiving ritonavir

- Adverse events should be reported to FDA Medwatch

Duration of Standing Order:

This Standing Order shall remain in effect for the duration of the FDA's EUA for treatment of COVID-19 using of Molnupiravir, and the duration of the PREP Act immunity provisions. This Standing Order shall automatically be rescinded upon the revocation of the FDA's EUA for treatment of COVID-19 using of Molnupiravir, or the expiration of the COVID-19 immunity protections for covered countermeasures under the PREP Act, or upon ending of the Public Health Emergency Declaration, whichever occurs first.

For questions or concerns regarding this document, please submit your inquiry to fernando.esteves@ghs.guam.gov.

*****SUBJECT TO CHANGE*****

FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF PAXLOVID FOR CORONAVIRUS DISEASE 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with PAXLOVID for the treatment of mild-to-moderate coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus. This Fact Sheet contains information to help you understand the risks and benefits of taking the PAXLOVID you have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make PAXLOVID available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). PAXLOVID is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about PAXLOVID. Talk to your healthcare provider about your options or if you have any questions. It is your choice to take PAXLOVID.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild-to-severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example seem to be at higher risk of being hospitalized for COVID-19.

What is PAXLOVID?

PAXLOVID is an investigational medicine used to treat mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (40 kg)] with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. PAXLOVID is investigational because it is still being studied. There is limited information about the safety and effectiveness of using PAXLOVID to treat people with mild-to-moderate COVID-19.

The FDA has authorized the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (40 kg)] with a positive test for the virus that causes COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death, under an EUA.

What should I tell my healthcare provider before I take PAXLOVID?

Tell your healthcare provider if you:

- Have any allergies
- Have liver or kidney disease
- Are pregnant or plan to become pregnant
- Are breastfeeding a child
- Have any serious illnesses

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with PAXLOVID and may cause serious side effects. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

You can ask your healthcare provider or pharmacist for a list of medicines that interact with PAXLOVID. **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take PAXLOVID with other medicines.

Tell your healthcare provider if you are taking combined hormonal contraceptive. PAXLOVID may affect how your birth control pills work. Females who are able to become pregnant should use another effective alternative form of contraception or an additional barrier method of contraception. Talk to your healthcare provider if you have any questions about contraceptive methods that might be right for you.

How do I take PAXLOVID?

- PAXLOVID consists of 2 medicines: nirmatrelvir and ritonavir.
    - Take 2 pink tablets of nirmatrelvir with 1 white tablet of ritonavir by mouth 2 times each day (in the morning and in the evening) for 5 days. **For each dose, take all 3 tablets at the same time.**
    - **If you have kidney disease, talk to your healthcare provider. You may need a different dose.**
- Swallow the tablets whole. Do not chew, break, or crush the tablets.
- Take PAXLOVID with or without food.
- Do not stop taking PAXLOVID without talking to your healthcare provider, even if you feel better.
- If you miss a dose of PAXLOVID within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of PAXLOVID at the same time.
- If you take too much PAXLOVID, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you are taking a ritonavir- or cobicistat-containing medicine to treat hepatitis C or Human Immunodeficiency Virus (HIV), you should continue to take your medicine as prescribed by your healthcare provider.

Talk to your healthcare provider if you do not feel better or if you feel worse after 5 days.

Who should generally not take PAXLOVID?

Do not take PAXLOVID if:

- You are allergic to nirmatrelvir, ritonavir, or any of the ingredients in PAXLOVID.
- You are taking any of the following medicines:
    - Alfuzosin
    - Pethidine, piroxicam, propoxyphene
    - Ranolazine
    - Amiodarone, dronedarone, flecainide, propafenone, quinidine
    - Colchicine
    - Lurasidone, pimozide, clozapine
    - Dihydroergotamine, ergotamine, methylergonovine
    - Lovastatin, simvastatin
    - Sildenafil (Revatio®) for pulmonary arterial hypertension (PAH)
    - Triazolam, oral midazolam
    - Apalutamide
    - Carbamazepine, phenobarbital, phenytoin
    - Rifampin
    - St. John's Wort (*hypericum perforatum*)

Taking PAXLOVID with these medicines may cause serious or life-threatening side effects or affect how PAXLOVID works.

These are not the only medicines that may cause serious side effects if taken with PAXLOVID. PAXLOVID may increase or decrease the levels of multiple other medicines. It is very important to tell your healthcare provider about all of the medicines you are taking because additional laboratory tests or changes in the dose of your other medicines may be necessary while you are taking PAXLOVID. Your healthcare provider may also tell you about specific symptoms to watch out for that may indicate that you need to stop or decrease the dose of some of your other medicines.

What are the important possible side effects of PAXLOVID?

Possible side effects of PAXLOVID are:

- **Liver Problems.** Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-colored urine, pale colored stools and itchy skin, stomach area (abdominal) pain.
- **Resistance to HIV Medicines**. If you have untreated HIV infection, PAXLOVID may lead to some HIV medicines not working as well in the future.

- **Other possible side effects include:**
  - altered sense of taste
  - diarrhea
  - high blood pressure
  - muscle aches

These are not all the possible side effects of PAXLOVID. Not many people have taken PAXLOVID. Serious and unexpected side effects may happen. PAXLOVID is still being studied, so it is possible that all of the risks are not known at this time.

What other treatment choices are there?
Like PAXLOVID, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice to be treated or not to be treated with PAXLOVID. Should you decide not to receive it or for your child not to receive it, it will not change your standard medical care.

What if I am pregnant or breastfeeding?
There is no experience treating pregnant women or breastfeeding mothers with PAXLOVID. For a mother and unborn baby, the benefit of taking PAXLOVID may be greater than the risk from the treatment. If you are pregnant, discuss your options and specific situation with your healthcare provider.

It is recommended that you use effective barrier contraception or do not have sexual activity while taking PAXLOVID.

If you are breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with PAXLOVID?
Contact your healthcare provider if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088 or you can report side effects to Pfizer Inc. at the contact information provided below.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

How should I store PAXLOVID?
Store PAXLOVID tablets at room temperature, between 68°F to 77°F (20°C to 25°C).

How can I learn more about COVID-19?
- Ask your healthcare provider.
- Visit https://www.cdc.gov/COVID19.
- Contact your local or state public health department.

What is an Emergency Use Authorization (EUA)?
The United States FDA has made PAXLOVID available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and children [12 years of age and older weighing at least 88 pounds (40 kg)] with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for PAXLOVID is in effect for the duration of the COVID-19 declaration justifying emergency use of this product, unless terminated or revoked (after which the products may no longer be used under the EUA).

Additional Information
For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

www.pfizermedinfo.com or call 1-800-438-1985 for more information.

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New York, NY 10017

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Revised: 22 December 2021

December 22, 2021

IMPORTANT PRESCRIBING INFORMATION

Subject: PAXLOVID Emergency Use Authorization (EUA) dosing and dispensing in moderate renal impairment, and risk of serious adverse reactions due to drug interactions

Dear Healthcare Provider,

The purpose of this letter is to make you aware of the EUA dosing and dispensing requirements for patients with moderate renal impairment, and the potential for drug-drug interactions associated with PAXLOVID (nirmatrelvir tablets; ritonavir tablets). PAXLOVID contains two different drugs that are co-packaged in a daily blister card for oral use.

The dosage for PAXLOVID is as follows:

eGFR*	**PAXLOVID Dose**
Greater than 60 mL/min (*normal renal function or mild renal impairment*)	300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
≥30 to <60 mL/min (*moderate renal impairment*)	150 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
<30 mL/min (*severe renal impairment*)	PAXLOVID is not recommended (the appropriate dose has not been determined).

*eGFR=estimated glomerular filtration rate based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula

Each daily blister card contains a morning and evening dose, with each dose consisting of 300 mg nirmatrelvir (two oval, pink 150 mg tablets) and 100 mg ritonavir (one ovaloid, white 100 mg tablet) as shown in Figure A below, which is incongruent with the moderate renal impairment dose.

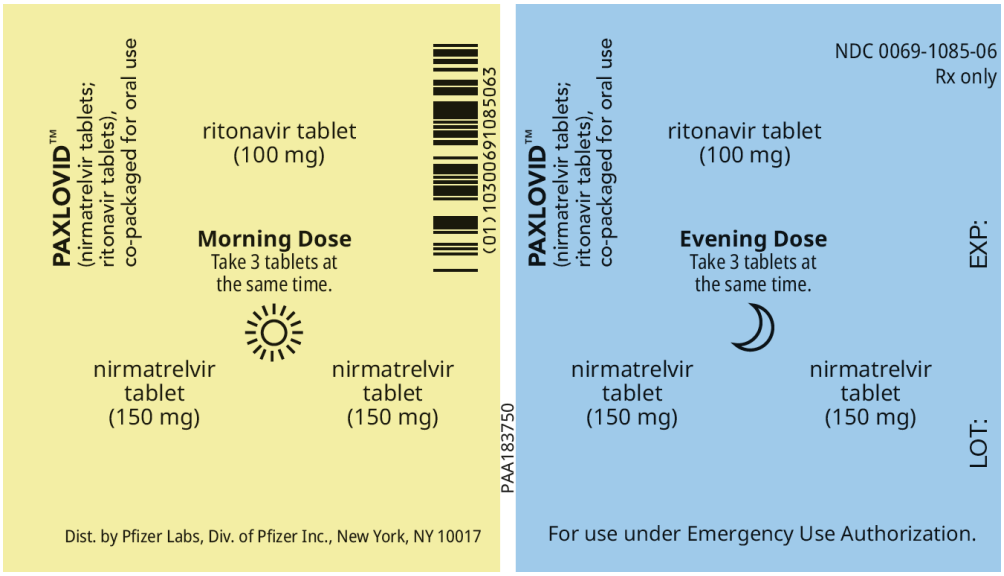


Figure A: Blister card containing morning and evening dose for normal renal function or mild renal impairment

Each daily blister card contains more nirmatrelvir tablets than are needed for dosing in patients with moderate renal impairment. **It is critical that all prescriptions specify the numeric dose for each active ingredient within PAXLOVID as follows:**

- **PAXLOVID 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment, or**
- **PAXLOVID 300 mg nirmatrelvir with 100 mg ritonavir for patients with normal renal function or mild renal impairment**

Dispensing information in patients with moderate renal impairment:

Each shipment of PAXLOVID will be accompanied with **instructions, for pharmacists to remove the unneeded, additional nirmatrelvir tablets, and with stickers to affix to each daily blister card as well as the carton** when dispensing PAXLOVID to patients with moderate renal impairment (see below for image of dispensing instructions).

Pharmacists should ensure that they refer to the instructions entitled “IMPORTANT PAXLOVID™ DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT” regarding specific instructions on tablet removal and proper sticker placement. In addition, **pharmacists should counsel patients** about renal dosing instructions and notify them that their blister cards have been altered at the pharmacy.

IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT

To dispense PAXLOVID dose (150 mg nirmatrelvir with 100 mg ritonavir) for moderate renal impairment, pharmacist should:

STEP ONE: Remove one of the 150 mg nirmatrelvir tablets from the morning dose and remove one of the 150 mg nirmatrelvir tablets from the evening dose of the blister card (see figure 1 below). The nirmatrelvir tablets that are removed should be the ones closest to the middle of the blister pack.

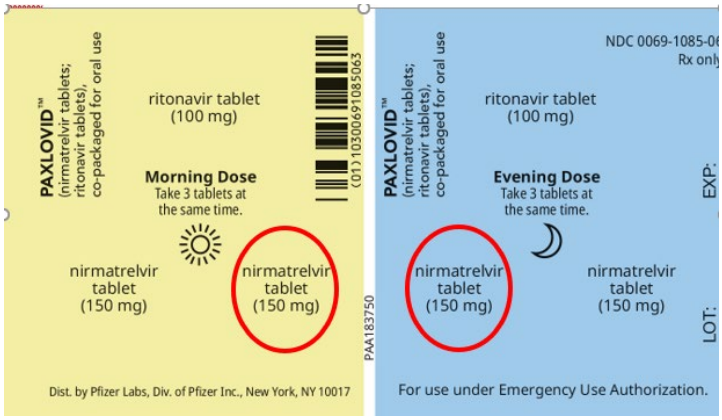


Figure 1: Remove the nirmatrelvir tablets circled in red from the blister card

STEP TWO: Affix the blister card with one sticker from the provided tear pad to carefully cover the empty blister cavities as shown in figure 2 below. The exact placement of this sticker is important to cover the empty blister cavities from the tablets. Ensure the sticker also covers the pre-printed dosing instruction that is on the blister card.

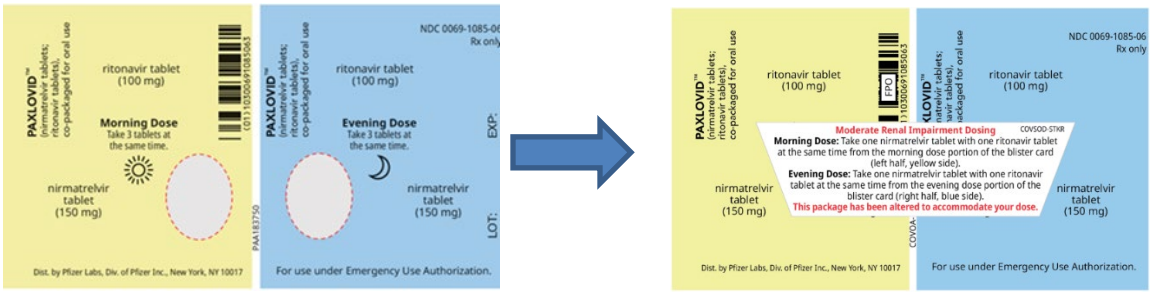


Figure 2: Placement of sticker over empty blister cavities and pre-printed dosing instruction after removal of nirmatrelvir tablets

STEP THREE: Repeat steps one and two for every blister card in the carton (each carton contains five blister cards for a full 5-day dosing regimen).

STEP FOUR: Affix one sticker from the provided tear pad to carefully cover over the pre-printed dosing regimen on the carton as shown in figure 3 below:

Figure 3: Placement of sticker over pre-printed dosing regimen on carton

Patients with moderate renal impairment should be instructed to take only one 150-mg nirmatrelvir tablet with one 100-mg ritonavir tablet together twice daily for 5 days. **Patients with moderate renal impairment should be notified that their blister cards have been altered by their pharmacist to remove unneeded tablets.**

Risk of Serious Adverse Reactions Due to Drug Interactions:

Use of PAXLOVID, a CYP3A inhibitor, in patients receiving concomitant medications metabolized by CYP3A may increase the plasma concentrations of those concomitant medications.

Use of concomitant medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

See the current EUA Fact Sheet for Healthcare Providers for clinically significant drug interactions, including **contraindicated** drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

Prescribers and pharmacists should inform patients that PAXLOVID may interact with some drugs and is **contraindicated** for use with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription or non-prescription medication or herbal products.

Indication & Authorized Use:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

Healthcare providers should consider the benefit-risk for an individual patient.

Limitations of Authorized Use:

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

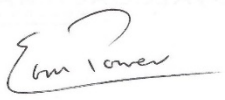
Reporting Adverse Events and Medication Errors:

Under the EUA, all serious adverse events and all medication errors potentially related to PAXLOVID must be reported.
Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 (https://www.fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 208529787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form. Please provide a copy of all FDA MedWatch forms to Pfizer via fax (1-866-635-8337), telephone (1-800-438-1985) or website www.pfizersafetyreporting.com

The PAXLOVID EUA Fact Sheet for Healthcare Providers is available at www.COVID19oralRx.com or by scanning the QR Code below:

Sincerely,



Eddie G M Power PhD MBA GFMD
Vice President, North America Medical Affairs

IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT

Attention Pharmacist:

Do not discard this page.

To dispense PAXLOVID dose (150 mg nirmatrelvir with 100 mg ritonavir) for moderate renal impairment, pharmacist should:

STEP ONE: Remove one of the 150 mg nirmatrelvir tablets from the morning dose and remove one of the 150 mg nirmatrelvir tablets from the evening dose of the blister card (see figure 1 below). The nirmatrelvir tablets that are removed should be the ones closest to the middle of the blister pack.

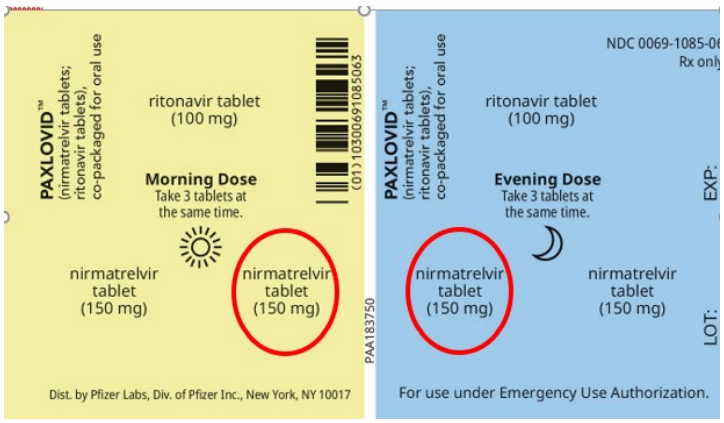


Figure 1: Remove the nirmatrelvir tablets circled in red from the blister card

STEP TWO: Affix the blister card with one sticker from the provided tear pad to carefully cover the empty blister cavities as shown in figure 2 below. The exact placement of this sticker is important to cover the empty blister cavities from the tablets. Ensure the sticker also covers the pre-printed dosing instruction that is on the blister card.

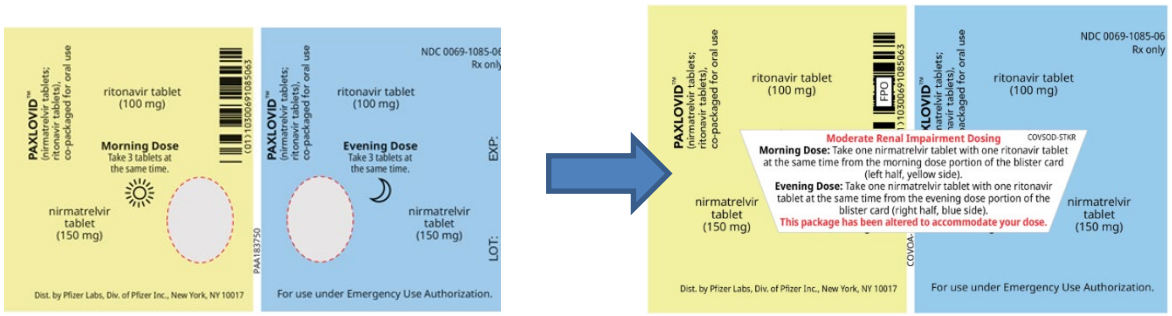


Figure 2: Placement of sticker over empty blister cavities and pre-printed dosing instruction after removal of nirmatrelvir tablets

STEP THREE: Repeat steps one and two for every blister card in the carton (each carton contains five blister cards for a full 5-day dosing regimen).

See reverse side for additional instructions.

STEP FOUR: Affix one sticker from the provided tear pad to carefully cover over the pre-printed dosing regimen on the carton as shown in figure 3 below:

Figure 3: Placement of sticker over pre-printed dosing regimen on carton

Patients with moderate renal impairment should be instructed to take only one 150-mg nirmatrelvir tablet with one 100-mg ritonavir tablet together twice daily for 5 days. **Patients with moderate renal impairment should be notified that their blister cards have been altered by their pharmacist to remove unneeded tablets.**

How to obtain additional stickers: Pharmacies needing additional pads should contact C19therapies@amerisourcebergen.com.

For further information, including how to report adverse events and all medication errors, please refer to the EUA Fact Sheet for Healthcare Providers.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use PAXLOVID™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PAXLOVID.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Original EUA Authorized Date: 12/2021

---------- EUA FOR PAXLOVID ----------
The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE
- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

PAXLOVID is not approved for any use, including for use as treatment of COVID-19. (1)

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

---------- DOSAGE AND ADMINISTRATION ----------
PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)
Nirmatrelvir must be co-administered with ritonavir. (2.1)
- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1)
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.2)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2.2, 8.6)
- PAXLOVID is not recommend in patients with severe hepatic impairment (Child-Pugh Class C). (2.3, 8.7)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Tablets: nirmatrelvir 150 mg (3)
- Tablets: ritonavir 100 mg (3)

----------CONTRAINDICATIONS----------
- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.2)
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. (5.3)

---------- ADVERSE REACTIONS ----------
Adverse events (incidence ≥1% and ≥5 subject difference) were dysgeusia, diarrhea, hypertension, and myalgia. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PAXLOVID (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Pfizer Inc. at fax number: 1-866-635-8337. (6.4)

----------DRUG INTERACTIONS----------
Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy. (2.4, 4, 5.1, 7, 12.3)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed.

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk[1] for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 *[see Dosage and Administration (2.1)]*.[2]
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a U.S. Food and Drug Administration authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

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[1] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

[2] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - the known and potential benefits of the product—when used to diagnose, prevent, or treat such disease or condition—outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There are no approved alternatives to PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Other therapeutics are currently authorized for the same use as PAXLOVID. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies that are testing the use of PAXLOVID in COVID-19, please see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of PAXLOVID

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

The dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next

dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Important Dosing Information in Patients with Renal Impairment

No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)].*

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

2.3 Use in Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

2.4 Important Drug Interactions with PAXLOVID

No dosage adjustment is required when co-administered with other products containing ritonavir or cobicistat.

Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

Refer to other sections of the Fact Sheet for important drug interactions with PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*

3 DOSAGE FORMS AND STRENGTHS

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side. Each tablet contains 150 mg of nirmatrelvir.

- Ritonavir is supplied as white film-coated ovaloid tablets debossed with the "a" logo and the code NK. Each tablet contains 100 mg of ritonavir.

4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.3)]*:

- Alpha$_1$-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]*:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (*hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for PAXLOVID. Serious and unexpected adverse events may occur that have not been previously reported with PAXLOVID use.

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of PAXLOVID, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.

- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

See Table 1 for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

5.2 Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

5.3 Risk of HIV-1 Resistance Development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection *[see Dosage and Administration (2.4), Contraindications (4), and Drug Interactions (7)]*.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of PAXLOVID that supported the EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Additional adverse events associated with PAXLOVID may become apparent with more widespread use.

The safety of PAXLOVID is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomized, placebo-controlled trial in non-hospitalized adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection *[see Clinical Studies (14.1)]*. A total of 2,224 symptomatic adult subjects 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either PAXLOVID (n=1,109) or placebo (n=1,115). Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. PAXLOVID [300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir] or matching placebo were to be taken twice daily for 5 days.

Adverse events (all grades regardless of causality) in the PAXLOVID group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%).

The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PAXLOVID within 7 calendar days from the onset of the event, using FDA Form 3500 (for information on how to access

this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race).
- A statement " PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's pre-existing medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: https://www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with PAXLOVID.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

7 DRUG INTERACTIONS

7.1 Potential for PAXLOVID to Affect Other Drugs

PAXLOVID (nirmatrelvir co-packaged with ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated *[see Contraindications (4) and Table 1]*. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

7.2 Potential for Other Drugs to Affect PAXLOVID

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides listing of clinically significant drug interactions, including contraindicated drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult appropriate references for comprehensive information *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Analgesics	pethidine, piroxicam, propoxyphene	↑ pethidine ↑ piroxicam ↑ propoxyphene	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities *[see Contraindications (4)]*.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	bepridil, lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)].*

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor INR if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin	↓ nirmatrelvir/ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole,	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir	↑ protease Inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use of these protease inhibitors *[see Dosage and Administration (2.4)].*
Anti-HIV	didanosine, delavirdine, efavirenz, maraviroc, nevirapine, raltegravir, zidovudine bictegravir/ emtricitabine/ tenofovir	↑ didanosine ↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide, clozapine	↑ lurasidone ↑ pimozide ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir.
	ombitasvir/paritaprevir/ritonavir and dasabuvir		Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information.
	sofosbuvir/velpatasvir/voxilaprevir		Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use *[see Dosage and Administration (2.4)]*.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	cyclosporine, tacrolimus, sirolimus	↑ cyclosporine ↑ tacrolimus ↑ sirolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and PAXLOVID. If co-administered, refer to individual product label for immunosuppressant for further information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic analgesics	fentanyl	↑ fentanyl	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with PAXLOVID.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
PDE5 inhibitor	sildenafil (Revatio®) when used for pulmonary arterial hypertension	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Sedative/hypnotics	triazolam, oral midazolam	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Sedative/hypnotics	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Systemic corticosteroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage *(see Data).* There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations).*

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 10 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

In animal reproduction studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at doses (based on body surface area conversions) or systemic exposures (AUC) greater than or equal to 3 times higher than clinical doses or exposure at the authorized human dose of PAXLOVID *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S.

general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Human Data

Ritonavir
Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,400 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.3% (95% confidence interval [CI]: 1.9%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.6%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir
Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and 6 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 10 times higher than clinical exposures at the authorized human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed at up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3 times higher than clinical exposures at the authorized human dose of PAXLOVID. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 is ongoing and only interim data through postnatal day (PND) 56 are currently available. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease (8% in males and females) in the body weight of offspring was observed at PND 17. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, resulting in systemic exposure

(AUC_{24}) approximately 5 times higher than clinical exposures at the authorized human dose of PAXLOVID.

Ritonavir
Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) approximately 4 times higher than exposure at the authorized human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures approximately 4 times higher than exposure at the authorized human dose of PAXLOVID. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the authorized human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the authorized human dose of PAXLOVID, based on a body surface area conversion factor. In a pre- and postnatal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through postnatal day 20 resulted in no developmental toxicity, at ritonavir doses 3 times higher than the authorized human dose of PAXLOVID, based on a body surface area conversion factor.

8.2 Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir *(see Data)*. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data
In the pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 8 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 5 times higher than clinical exposures at the authorized human dose of PAXLOVID.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as observed in adults, and adults with similar body weight were included in the trial EPIC-HR *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Of the total number of subjects in EPIC-HR randomized to receive PAXLOVID (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

8.6 Renal Impairment

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment *[see Clinical Pharmacology (12.3)].*

No dosage adjustment is needed in patients with mild renal impairment. In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dose of PAXLOVID to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. *Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)].*

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

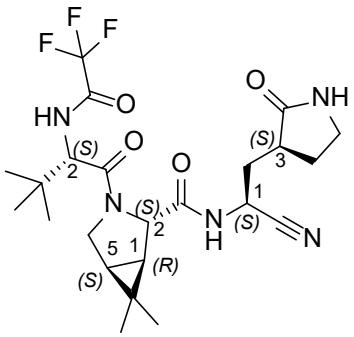
Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

11 DESCRIPTION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

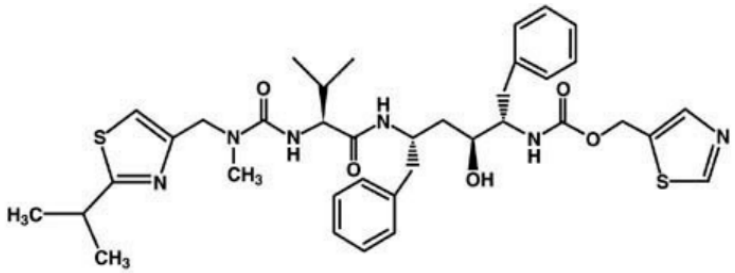
The chemical name of active ingredient of nirmatrelvir is (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide]. It has a molecular formula of $C_{23}H_{32}F_3N_5O_4$ and a molecular weight of 499.54. Nirmatrelvir has the following structural formula:



Nirmatrelvir is available as immediate-release, film-coated tablets. Each tablet contains 150 mg nirmatrelvir with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

Ritonavir

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is available as film-coated tablets. Each tablet contains 100 mg ritonavir with the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The following are the ingredients in the film coating: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 Mpro in a biochemical assay with a K_i value of 3.1 nM and an IC_{50} value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 Mpro active site by X-ray crystallography.

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

12.3 Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy subjects.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir, thereby supporting a twice daily administration regimen.

Upon oral administration of nirmatrelvir/ritonavir, the increase in systemic exposure appears to be less than dose proportional up to 750 mg as a single dose and up to 500 mg twice daily as multiple doses. Twice daily dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. The pharmacokinetic properties of nirmatrelvir/ritonavir are displayed in Table 2.

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (h), median	3.00[a]	3.98[a]
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[c]
V_z/F (L), mean	104.7[b]	112.4[b]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F), mean	8.99[b]	13.92[b]
Metabolism		
Metabolic pathways	Minimal[d]	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	49.6%[e]	86.4%[f]
% drug-related material in urine	35.3%[e]	11.3%[f]

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
c. Red blood cell to plasma ratio.
d. Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.
e. Determined by ^{19}F-NMR analysis following 300 mg oral suspension enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution.

Single dose pharmacokinetic data of PAXLOVID in healthy subjects is depicted below (Table 3).

Table 3: Single Dose Pharmacokinetics of Nirmatrelvir Following Dosing with 300 mg/100 mg Nirmatrelvir/Ritonavir in Healthy Subjects

PK Parameter (units)	Nirmatrelvir (N=12)
C_{max} (µg/mL)	2.21 (33)
AUC_{inf} (µg*hr/mL)	23.01 (23)
T_{max} (hr)	3.00 (1.02-6.00)
$T_{1/2}$ (hr)	6.05 ± 1.79

Represents data from 2 x 150 mg tablets of nirmatrelvir. Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $T_{1/2}$.

Effect of Food on Oral Absorption of Nirmatrelvir
Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir co-administered with ritonavir tablets.

Specific Populations

The pharmacokinetics of nirmatrelvir/ritonavir based on age and gender have not been evaluated.

Pediatric Patients
The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been evaluated.

Using a population PK model, the dosing regimen is expected to result in comparable steady-state plasma exposure of nirmatrelvir in patients 12 years of age and older and weighing at least 40 kg to those observed in adults after adjusting for body weight.

Racial or Ethnic Groups
Systemic exposure in Japanese subjects was numerically lower but not clinically meaningfully different than those in Western subjects.

Patients with Renal Impairment
An open-label study compared nirmatrelvir/ritonavir pharmacokinetics in healthy adult subjects and subjects with mild (eGFR ≥60 to <90 mL/min), moderate (eGFR ≥30 to <60 mL/min), and severe (eGFR <30 mL/min) renal impairment following administration of a single oral dose of nirmatrelvir 100 mg enhanced with ritonavir 100 mg administered at -12, 0, 12, and 24 hours. Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87%

higher, and in patients with severe renal impairment was 48% and 204% higher, respectively (Table 4).

Table 4: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Patients with Hepatic Impairment
A single oral dose of 100 mg nirmatrelvir enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours and 24 hours in subjects with moderate hepatic impairment resulted in similar exposures compared to subjects with normal hepatic function (Table 5).

Table 5: Impact of Hepatic Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Hepatic Function (n=8)	Moderate Hepatic Impairment (n=8)
C_{max} (µg/mL)	1.89 (20)	1.92 (48)
AUC_{inf} (µg*hr/mL)	15.24 (36)	15.06 (43)
T_{max} (hr)	2.0 (0.6 - 2.1)	1.5 (1.0 - 2.0)
$T_{1/2}$ (hr)	7.21 ± 2.10	5.45 ± 1.57

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Drug Interaction Studies Conducted with Nirmatrelvir

In vitro data indicates that nirmatrelvir is a substrate for human MDR1 (P-gp) and 3A4, but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Nirmatrelvir does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro* at clinically relevant concentrations. Nirmatrelvir has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp).

Nirmatrelvir does not induce any CYPs at clinically relevant concentrations.

Drug Interaction Studies Conducted with Ritonavir

In vitro studies indicate that ritonavir is mainly a substrate of CYP3A. Ritonavir also appears to be a substrate of CYP2D6 which contributes to the formation of isopropylthiazole oxidation metabolite M-2.

Ritonavir is an inhibitor of CYP3A and to a lesser extent CYP2D6. Ritonavir appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

The effects of co-administration of PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarized in Table 6 (effect of other drugs on nirmatrelvir).

Table 6: Drug Interactions: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the Co-administered Drugs

Co-administered Drug	Dose (Schedule)		N	Ratio (in combination with Co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg twice daily (5 doses)	9	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=maximum plasma concentrations.

a. For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

12.4 Microbiology

Antiviral Activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC_{50} and EC_{90} values of 62 nM and 181 nM, respectively, after 3 days of drug exposure.

Nirmatrelvir had similar cell culture antiviral activity (EC_{50} values ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

No data are available regarding the activity of nirmatrelvir against the SARS-CoV-2 Omicron (B.1.1.529) variant in cell culture. However, in a biochemical assay, the Mpro P132H substitution found in the Omicron variant did not reduce nirmatrelvir activity (K_i fold change <1) compared to the USA-WA1/2020 enzyme.

Antiviral Activity Against SARS-CoV-2 in Animal Models

Nirmatrelvir showed antiviral activity in BALB/c and 129 mice infected with mouse-adapted SARS-CoV-2. Oral administration of nirmatrelvir at 300 mg/kg or 1,000 mg/kg twice daily initiated 4 hours post-inoculation or 1,000 mg/kg twice daily initiated 12 hours post-inoculation resulted in reduction of lung viral titers and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals.

Antiviral Resistance

Phenotypic assessments were conducted to characterize the impact of naturally occurring SARS-CoV-2 Mpro polymorphisms on the activity of nirmatrelvir in a biochemical assay using recombinant Mpro enzyme. The clinical significance of these polymorphisms is unknown, and it is also unknown if results from the biochemical assay are predictive of antiviral activity in cell culture. The following Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (≥3-fold higher K_i values): G15S (4.4-fold), T135I (3.5-fold), S144A (91.9-fold), H164N (6.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). G15S is present in the Lambda variant, which did not have reduced susceptibility to nirmatrelvir (relative to USA-WA1/2020) in cell culture.

In addition, three SARS-CoV-2 Mpro amino acid positions where polymorphisms have not been naturally observed were evaluated by substituting alanine at these positions and assessing their impact on activity in biochemical assays. These Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (i.e., higher K_i values): Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). The clinical significance of substitutions at these Mpro positions is unknown.

Cell culture resistance selection studies with nirmatrelvir using mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions P15A, T50K, P55L, T129M, and/or S144A. The clinical relevance of these changes is not known. The presence of the substitutions P55L and S144A was associated with reduced nirmatrelvir susceptibility (~4- to 5-fold higher EC_{50} values). These positions correspond to E55 and S144 in SARS-CoV-2 Mpro, respectively. E55L alone did not affect nirmatrelvir activity against SARS-CoV-2 Mpro in a biochemical assay, while S144A reduced nirmatrelvir activity by 91.9-fold (based on K_i value).

Limited SARS-CoV-2 sequencing data are available to characterize nirmatrelvir resistance in clinical trials. The SARS-CoV-2 Mpro substitutions A260V (n=3) or A260T (n=1) emerged in 4% (4/97) of nirmatrelvir/ritonavir treated subjects in clinical trial EPIC-HR with available sequence analysis data. A260T and A260V substitutions are infrequent natural polymorphisms in publicly available SARS-CoV-2 sequences (as of Dec 5, 2021). In a biochemical assay, the A260V Mpro substitution did not reduce nirmatrelvir activity (K_i fold-change <1).

Cross-resistance is not expected between nirmatrelvir and anti-SARS-CoV-2 monoclonal antibodies or remdesivir based on their different mechanisms of action.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nirmatrelvir

Carcinogenicity studies have not been conducted with nirmatrelvir.

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for

males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in systemic exposure (AUC_{24}) approximately 4 times higher than exposure at the authorized human dose of PAXLOVID.

Ritonavir

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 2 times higher (in males) than the exposure in humans at the authorized human dose of PAXLOVID. There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 4 times higher (in females) than the exposure in humans at the authorized human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 36% that of the exposure in humans at the authorized human dose of PAXLOVID.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 2 (male) and 4 (female) times higher than the exposure in humans at the authorized human dose of PAXLOVID.

13.2 Animal Toxicology and/or Pharmacology

Studies with nirmatrelvir included repeat dose toxicity studies in rats (14 days) and monkeys (15 days). Repeated daily oral dosing in rats at up to 1,000 mg/kg/day resulted in non-adverse hematological, liver, and thyroid effects. All of the hematology and coagulation findings (i.e., increases in PT and APTT) had no clinical or microscopic correlates and all findings completely recovered at the end of the 2-week recovery period. The liver (i.e., minimal to mild periportal hepatocyte hypertrophy and vacuolation) and thyroid gland (i.e., thyroid follicular cell hypertrophy) findings were consistent with secondary adaptive effects related to microsomal enzyme-induced increase in thyroid hormone clearance in the liver, a mechanism that rats are known to be particularly sensitive to relative to humans. All of the findings observed in the liver and thyroid were low severity and occurred in the absence of correlating alterations in clinical pathology parameters, and all of these findings fully recovered. No adverse effects were observed at doses up to 1,000 mg/kg/day, resulting in systemic exposure approximately 4 times higher than exposures at the authorized human dose of PAXLOVID. Nirmatrelvir-related findings following repeat oral dosing in monkeys for 15 days were limited to emesis and increase in fibrinogen. Increased fibrinogen may be attributed to an inflammatory state but lacked a microscopic correlate. At the high dose of 600 mg/kg/day, the systemic exposure in monkeys was about 18 times higher than exposures at the authorized human dose of PAXLOVID.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk of Progressing to Severe COVID-19 Illness

The data supporting this EUA are based on the analysis of EPIC-HR (NCT04960202), a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of

age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The study excluded individuals with a history of prior COVID-19 infection or vaccination. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set (all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,246 subjects were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 46 years; 51% were male; 72% were White, 5% were Black, and 14% were Asian; 45% were Hispanic or Latino; 66% of subjects had onset of symptoms ≤3 days from initiation of study treatment; 47% of subjects were serological negative at baseline; the mean (SD) baseline viral load was 4.63 $\log_{10}$ copies/mL (2.87); 26% of subjects had a baseline viral load of >10^7 (units); 6% of subjects either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization and were excluded from the mITT and mITT1 analyses.

The baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

Table 7 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 88% (95% CI: 75%, 94%).

Table 7: Efficacy Results in Non-Hospitalized Adults with COVID-19 Dosed within 5 Days of Symptom Onset who Did Not Receive COVID-19 Monoclonal Antibody Treatment at Baseline (mITT1 Analysis Set)

	PAXLOVID (N=1,039)	**Placebo** (N=1,046)
COVID-19 related hospitalization or death from any cause through Day 28		
n (%)	8 (0.8%)	66 (6.3%)
Reduction relative to placebo[a] [95% CI], %	-5.62 (-7.21, -4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval.

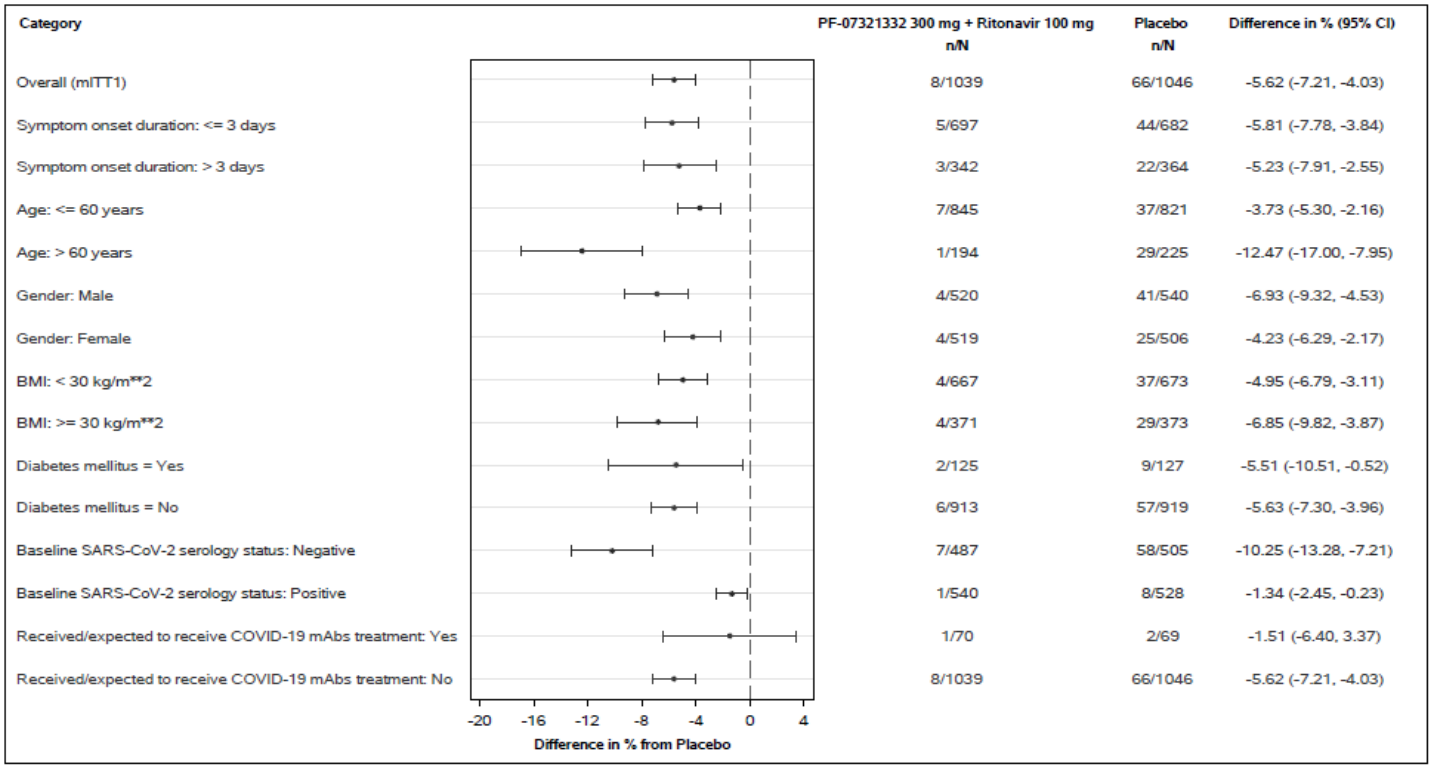
The determination of primary efficacy was based on a planned interim analysis of 780 subjects in mITT population. The estimated risk reduction was -6.3% with a 95% CI of (-9.0%, -3.6%) and 2-sided p-value <0.0001.

a. The estimated cumulative proportion of participants hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Consistent results were observed in the mITT and mITT2 analysis populations. A total of 1,379 subjects were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the PAXLOVID group, and 44/682 (6.45%) in the placebo group. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I.

Similar trends have been observed across subgroups of subjects *(see Figure 1)*. These subgroup analyses are considered exploratory.

Figure 1: Adults with COVID-19 Dosed within 5 Days of Symptom Onset with COVID-19-Related Hospitalization or Death from Any Cause Through Day 28 (Protocol C4671005)



N=number of participants in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on Normal approximation of the data are presented.

Relative to placebo, PAXLOVID treatment was associated with an approximately 0.9 $\log_{10}$ copies/mL greater decline in viral RNA levels in nasopharyngeal samples through Day 5, with similar results observed in the mITT, mITT1, and mITT2 analysis populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir tablets, 150 mg are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.
- Ritonavir tablets, 100 mg are white film-coated ovaloid tablets debossed with the "a" logo and the code NK.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

Each carton contains 30 tablets divided in 5 daily-dose blister cards (NDC number: 0069-1085-30).

Each daily blister card (NDC number: 0069-1085-06) contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening.

Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of PAXLOVID.

Use in Patients with Renal Impairment

No dose adjustment is needed in patients with mild renal impairment.

To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days. Instruct patients that the pharmacist will alter their daily blister cards to ensure they receive the correct dose.

Pharmacist should refer to the provided instructions entitled "IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT" for dispensing of PAXLOVID to patients with moderate renal impairment *[see Dosage and Administration (2.2)]*.

Appropriate dosage for patients with severe renal impairment has not been determined *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Drug Interactions

Inform patients that PAXLOVID may interact with some drugs and is contraindicated for use with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication, or herbal products *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*

Administration Instructions

Inform patients to take PAXLOVID with or without food as instructed. Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets. Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2. If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take

the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

For Medical Information about PAXLOVID, please visit www.pfizermedinfo.com or call 1-800-438-1985.

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